REMARKS

In the Office Action dated December 30, 2003, claims 1-31, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-31 are currently pending in this application and claims 32-40 have been withdrawn.

The office action indicates that the applicant has constructively elected claims 1-31 for prosecution. Applicants respectfully contend that when searching the claims originally on file, the examiner would have necessarily had to search the compounds recited in the pharmaceutical composition claims. Thus, examining the method and composition claims together would not constitute an undue burden on the Office.

Claims 2-6 and 9-12 were objected to as being of improper dependent form. These claims have been amended so that they no longer depend from claim 1. In addition, claim 16 was objected to due to a spelling error. Claim 16 has been amended to correct this error. In view of these amendments, applicants request that this objection be withdrawn.

Claims 1-31 were rejected under 35 USC §112, second paragraph, as indefinite. Claim 1 has been amended to further define the terms "ganglioside derivative" and "cholesterol derivative." Support for this language can be found on page 5, lines 20-24 and on page 7, lines 4-7 of the specification.

In addition, applicants point out that the office action is essentially imposing a requirement that an applicant prepare an application that is void of any generic terms, but instead lists any potential species that falls within the scope of a generic term and claims only those species. 35 U.S.C. §112, second paragraph does not impose such a requirement. The primary purpose of 35 U.S.C. §112, second paragraph is to ensure that the claim language is sufficiently precise so that a person skilled in the art can determine the boundaries of the claim. In the present case, the reference to "derivatives" in the claims in combination with the numerous examples given in the specification, appraise a person skilled in the art of the boundaries of the present invention. The fact that the compounds listed in the specification are examples, rather than a comprehensive list of the derivatives in question, does not make any claim supported by those examples less definite. These examples are provided to help one skilled in the art interpret and readily ascertain the scope of the claims and make and use the claimed invention. In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

The term "long chain" in claim 19, "wherein said functional group is . . . " in claim 22, "substituted" in claim 23 and claim 27 and "short fatty acid" in claim 30 were also found indefinite. Claim 19 has been amended incorporating the limitations of claims 20 and 21. Claim 22 has been amended to recite the functional groups in claim 23. Claim 30 has been amended to recite "C_2-C_{18} fatty acid". This amendment is supported by the disclosure on page 5, line 3 of the present application. Regarding the term "substituted", applicants contend that

the term "substituted alkyl" in claim 23 clearly refers to a "halide substituted alkyl," which is a well known term in the art and thus is not indefinite. Regarding claim 27, one would know that the organic group is substituted for another group in a basic cholesterol molecule as described on page 7, first paragraph of the present application. In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Claim 15 was rejected under 35 USC §103(a) as unpatentable over Ladisch. Applicants previously pointed out that Ladisch does not teach the administration of gangliosides, ganglioside derivatives and/or cholesterol derivatives in the amounts specified or the modulation of sphingolipid-cholesterol microdomains. Ladisch discloses only the addition of cholesterol (not cholesterol derivatives) to lipid emulsions to adjust a biologically normal relation of cholesterol/lecithin. Applicants point out that the administration of cholesterol would not produce the results obtained with the present invention. Cholesterol is not specific for microdomains and thus no imaginable dose would be pharmaceutically relevant to microdomain modifications. In the present invention, gangliosides, ganglioside derivatives and/or cholesterol derivatives are administered to produce the desired effect. Applicants point out that Ladisch teaches that certain lipids, particularly cholesterol, exchange freely between cells and their environment. This exchange is not found with gangliosides and thus the gangliosides, and ganglioside derivatives used in the present invention are not equivalent to the cholesterol used by Ladisch. Therefore, Ladisch does not teach all the elements of claim 15, in particular:

(1) the modulation of cholesterol-lipid microdomains of a cell membrane;

(2) the administration of the claimed amounts of gangliosides, ganglioside derivatives and/or cholesterol derivatives.

The office action appears to contend that the disclosure of the "change of the lipid composition of cell membranes" encompasses "modulation of cholesterol-lipid microdomains" and thus this broad recitation can be used to support an obviousness rejection. Applicants point out that even if Ladisch's change of the lipid composition of a cell membrane could broadly encompass the "modulation of cholesterol- lipid microdomains," (which it does not), there is no motivation or suggestion in the prior art to modulate the claimed "cholesterol-lipid microdomains,". Ladisch suggests only changing the lipid composition of the cell membrane in general.

Applicant's point out that Ladisch teaches "small amounts" of cholesterol (column 3, line 13) in a lipid emulsion (See the example and claims, which specify that cholesterol only constitutes a small percentile of the lipid emulsion). The office action has not shown how, in view of this disclosure, a person skilled in the art can arrive at the dosage limitations of 3mg to 30mg of cholesterol derivative per kg body weight/day currently recited in claim 15. The amount of cholesterol in Ladisch is kept low for a reason, Ladisch was only trying to avoid cholesterol depletion in cell membranes as a consequence of administration of a lipid emulsion. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 1-31 were rejected under 35 USC §103(a) as unpatentable over Brown and Rietveld et al. in view of U.S. Patent No. 4,551,449 to Ladisch. The Brown reference focuses on sphingolipid rafts and the interaction of other membrane lipids, in particular, cholesterol, with those rafts. Brown also teaches that cholesterol can promote phase separation, that is, the segregation of lipid components into domains that have different chemical compositions. This segregation has as a consequence that the physical properties of the resulting sphingolipid-cholesterol enriched phases change. Brown does not teach that the addition of cholesterol derivatives, a ganglioside or ganglioside derivative, after the sphingolipid-cholesterol enriched phase has been formed, would modulate this phase. Though Brown teaches that high cholesterol in a sphingolipid microdomain could create an environment that could be regulated to facilitate the diffusion of GPI-anchored proteins into or out of such domains, Brown does not make clear how this regulation could be accomplished. Thus, there is no motivation provided to add cholesterol derivatives, a ganglioside or ganglioside derivative to a sphingolipid-cholesterol microdomain to modulate such domains, and certainly not the location of components of such domains. In addition, there is no expectation of success of the present invention in view of Brown's disclosure. Brown is completely silent as to the addition of gangliosides or ganglioside derivatives to any type of domain.

Rietveld was cited primarily for showing that TX-100 extraction yielded a detergent insoluble glycolipid complex (DIG) in which GPI-anchored proteins were enriched together with sphingomyelin (SM) and cholesterol and does not

cure the deficiencies in Brown. Applicants point out that there is no teaching in Rietveld that the "accumulation" of cholesterol as discussed in Rietveld (page 472, second paragraph) is caused by adding cholesterol, and certainly not by adding cholesterol derivatives. Even if Rietveld suggested the addition of cholesterol, Rietveld indicates that it would stabilize the sphingolipid-cholesterol domains. In contrast to this, the inventors of the present invention have discovered that the opposite is true with cholesterol derivatives, gangliosides or ganglioside derivatives. That is, that the addition of cholesterol derivatives, gangliosides or ganglioside derivatives to cells increases the detergent solubility of proteins associated with such domains. This unexpected effect of external gangliosides, ganglioside derivatives and cholesterol derivatives allows one to modulate microdomains. In addition, there is no suggestion in Rietveld or Brown that the administration of gangliosides, ganglioside derivatives and/or cholesterol derivatives to a patient would have the desired results.

Ladisch does not cure the deficiencies in the Brown and Rietveld references as Ladisch discloses only the addition of cholesterol (not cholesterol derivatives) to lipid emulsions to adjust a biologically normal relation of cholesterol/lecithin. Applicants respectfully point out that all of the cited references refer to "cholesterol," while the claims of the current application recite gangliosides, ganglioside derivatives and/or cholesterol derivatives. In view of the fact that none of the cited references suggest or disclose that the administration of gangliosides, ganglioside derivatives and/or cholesterol

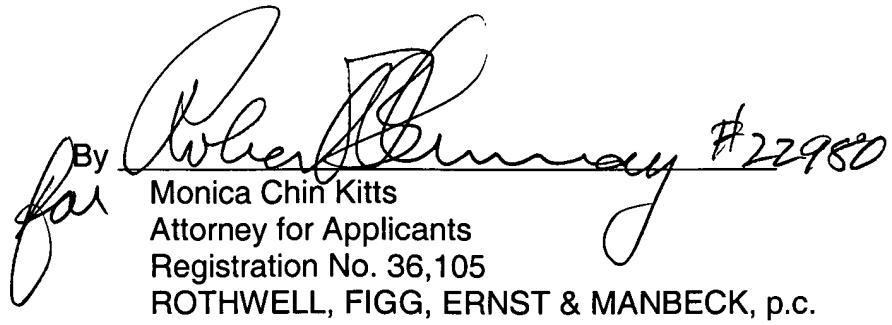
derivatives to a patient for modulating sphingolipid-cholesterol microdomains, applicants request that this rejection be withdrawn.

Applicants respectfully contend that Brown and Rietveld are newly cited references and thus the rejections should not have been made final. The claims were previously amended to clarify issues raised in the March 11, 2003 office action and thus should not have required a further search. In view of this, applicants request that the finality of the present office action be withdrawn or alternatively that the above claim amendments be entered.

Applicants respectfully submit that all of claims 1-40 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By  #22980

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